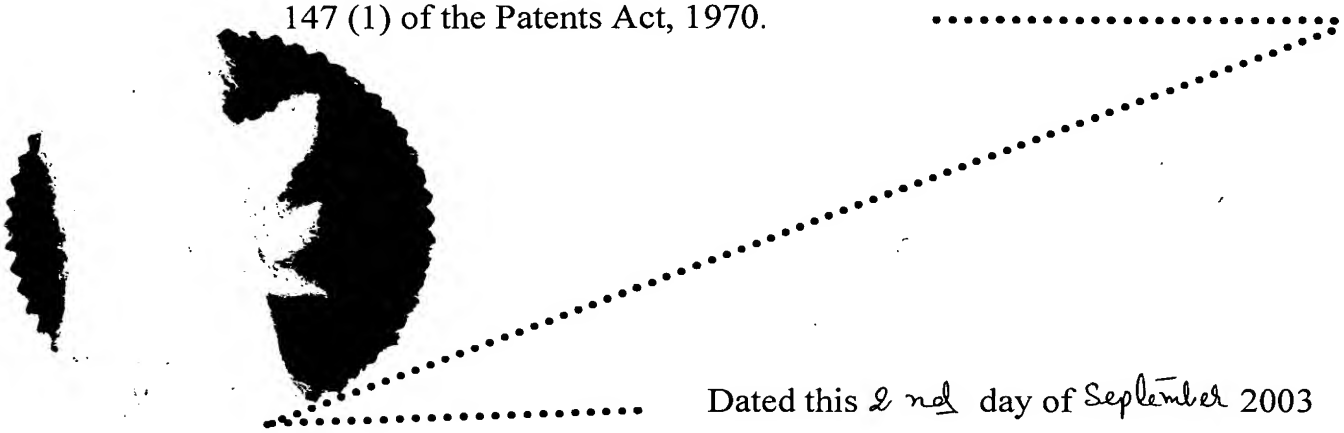
THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 22.01.2003 in respect of Patent Application No. 81/MUM/2003 of Torrent Pharmaceuticals Ltd., a company incorporated under the Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad – 380 009, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



Dated this 2nd day of September 2003

M.A. Haafeez.

(M.A. HAAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT

(See Sections 5(2), 7, 54 and 135 AND Rule 33A)

(1) We, **TORRENT PHARMACEUTICALS LTD.**, a company incorporated under Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad-380 009, India,

(2) hereby declare –

(a) We are in possession of an invention titled

"NEW DRUG DELIVERY SYSTEM"

(b) Provisional Specification relating to this invention is filed with this application;

(c) that there is no lawful ground of objection to the grant of a patent to us.

ORIGINAL

(3) further declare that the inventor for the said invention is:

NADKARNI, Sunil, Sadanand, an Indian citizen, of Torrent Research Centre, Torrent Pharmaceuticals Ltd., Bhat, Gandhinagar, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country, particulars of which are as follows:

NIL

(5) That we are the assignees of the true and first inventor.

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
E 556, Greater Kailash II,
New Delhi - 110 048, India.
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(7) The following declaration was given by the true and first inventors:

I, **NADKARNI, Sunil, Sadanand**; an Indian citizen, of Torrent Research Centre, **Torrent Pharmaceuticals Ltd.**, Bhat, Gandhinagar, Gujarat, India; the true and first inventor declare the applicants herein are my assignees:

81/MUM/2003
22/1/2003

SUNIL SADANAND NADKARNI

(8) that to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to me/us on this application.

(9) Following are the attachments with this application:

(a) PROVISIONAL specification in triplicate
(b) Form 1 in triplicate
(c) Form 2 in triplicate
(d) Statement and Undertaking on FORM 3 in duplicate
(e) Drawing in triplicate
(f) Abstract

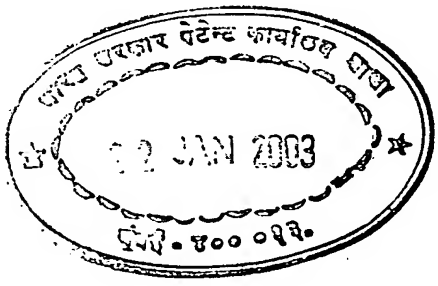
Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No.....
dated..... On .....Bank.

We request that a patent be granted to us for the said invention.

Dated this the 21th day of January 2003

For **TORRENT PHARMACEUTICALS LTD.**

The Controller of Patents
The Patent Office,
At Mumbai



Form 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(Section 10)

ORIGINAL

"New Drug Delivery System"

We, **Torrent Pharmaceuticals Ltd.,** a company incorporated under the Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad-380 009, Gujarat, India,

The following specification particularly describes the invention:

NEW DRUG DELIVERY SYSTEM

FIELD OF INVENTION

This invention relates to a modified release dosage form comprising of a high solubility active ingredient, which utilizes dual retard technique to effectively reduce the quantity of release controlling agents; a process for preparing the formulation.

BACKGROUND OF THE INVENTION

It is well known to those skilled in the art that the blood levels of drugs need to be maintained above a minimum effective level and below its minimum toxic level in order to obtain the desired therapeutic effects and to minimize side effects. Unfortunately, the pharmacokinetic properties (absorption, elimination and metabolism) of most drugs are such that they need to be administered three to four times a day. This kind of a dosing regimen is very inconvenient and leads to reduction in patient compliance. Reduction of dosing regimen from three times a day (t.i.d.) to twice daily (b.i.d.) to once a day results in increased convenience and comfort and therefore increased patient compliance. Drugs that are administered in the form of conventional tablets of capsules become available to body fluids at a rate that is initially very high, followed by a rapid decline. For many drugs, this delivery pattern results in a transient overdose, followed by a long period of under dosing. This is a pattern of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of modified delivery systems. Modified release formulations, which are effective in maintaining the therapeutic blood levels over, extended periods of time result in optimal therapy. They not only reduce the frequency of dosing, but they also reduce the severity and frequency of side effects, as they maintain substantially constant blood levels and avoid the fluctuations associated with the conventional immediate release formulations administered three to four times a day.

There are a number of different modified release dosage forms available commercially. However, some of these are expensive to manufacture and can be difficult to swallow,

particularly in elderly patients. Many of these modified delivery systems utilize hydrophilic, polymeric matrices

that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the release rate, instead resulting in a release that approximates first-order kinetics and may have a problem of dose dumping or burst release. However, since many modified release dosage forms contain comparatively large amounts of active ingredient it is often necessary to include large amounts of suitable excipients to achieve appropriate controlled release profiles. Clearly, this will tend to increase the size of the dosage form.

The various techniques to make modified release dosage form of drugs as described in prior art are as follows-

One method of prolonging the release of a highly water-soluble drug is disclosed PCT Patent application no. WO99/47128. A biphasic controlled release delivery system for metformin hydrochloride, which has prolonged gastric residence and that swells following hydration. The ratio of inner solid phase to outer continuous phase is 0.5:1 to about 4:1. The major limitation of this invention is that it provides a very bulky formulation for higher doses of the metformin that is very inconvenient for human consumption. For instance, example cited provides formulation of 500 mg metformin hydrochloride with tablet weight of 1.0 gm. Hence restricting to the low dose sustained release tablets of 500 mg or slightly more and making it obligatory to take two tablets of 500 mg each time to provide sustain action. The cited example teaches use of combination of atleast one hydrophilic polymer and which is a essential part for swelling. Non swellable or nonerodeble formulations are not included in the invention.

Whilst PCT application No. WO 02/28181 a1 describes a monolithic sustained release formulation of metformin hydrochloride. The method of making the formulation involves hot melt granulation followed by wet granulation with binders or extrusion. The formulation essentially requires binder and auxiliary pharmaceutically acceptable excipients. The formulation consists of metformin hydrochloride polymer and or hydrophobic material. The dosage form release more than 90% of the drug within 8 hours.

Similarly US patent no. 6340475 B2 assigned to Depomed Inc. describes monolithic controlled release formulation of

highly water soluble drugs including metformin hydrochloride. The formulation swells when ingested thus prolongs its residence time in the stomach. The formulations are made of hydrophilic polymers, which results in swellable and erodible matrix.

Another method of prolonging the release of a highly water-soluble drug is disclosed in International Patent application publication no. WO 96/26718, published Sep. 6, 1996. The method of this publication is the corporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet erodible in gastric fluids.

Similarly Chih-Ming Chen in international patent application number WO 02/36100 describes a once a formulation of metformin which is based on osmotically controlled technique and that is non expandable in nature and has a passage in the coating membrane for release of drug.

Kim et al. In United States patent number 6337091 describes a matrix based controlled release formulation for highly soluble drugs over long periods of time. The release controlling agent is a swellable gum which encapsulates or make granules of drug, which is then disposed in more swellable erodible polymers such as HPMC or poly(ethyleneoxide).

Whilst these systems can provide for modified release for selected active ingredients like active ingredients with low dose or low water solubility. When a highly soluble or high dose active ingredient is used, most of these systems have the disadvantages such as comparatively low payload of active ingredient thus making dosage form bulky and expensive or lead to burst effect or prolonged release of active ingredient for a shorter duration or use of complex manufacturing procedure and/or equipment.

There exists a need for compositions and process for making orally deliverable dosage form containing highly soluble active ingredient as modified release that overcomes the problems discussed above. This invention addresses the need.

Therefore, it would be of considerable clinical benefit to design a dosage form with high pay load of highly soluble active ingredient that would be much easier for the patient to swallow. This type of technology could also be used to reduce the size of many existing drug formulations.

Therefore an objective of the present invention is a modified release dosage form of high solubility active ingredient.

The second objective of the present invention is a modified release dosage form with high payload of active ingredient, which is suitable for swallowing for humans.

Accordingly, an object of the present invention is to have a dosage form, which uses dual retard technique to control the release of the high solubility active ingredient and significantly reduce the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing.

A further objective of the present invention is to have a dosage form, which gives accurate dosing and is prepared by conventional and simple processes.

A further objective of the present invention is to have a dosage form, which can be given twice a day or more preferably can be given once a day.

BRIEF DESCRIPTION OF THE INVENTION

The above objects are realized by a dosage form, which comprises of a) Micro matrix particles containing high solubility active ingredient and one or more hydrophobic release controlling agent, b) Coating of Micro matrix particles with one or more hydrophobic release controlling agents. It may optionally also include one or more commonly used excipients in oral pharmaceutical formulations. The present invention also provides solid oral dosage form comprising a composition according to the invention.

The present invention also teaches the use of dual retard technique to effectively control the release rate of modified release active ingredient by using small quantity of release controlling agents. This dual retard technique thus sufficiently reduces the size of the dosage form, which is convenient for swallowing.

The present invention further teaches the use of hydrophobic release controlling agents.

The present invention further provides a method of treating an animal, particularly a human in need of treatment

utilizing the active agents, comprising administering a therapeutically effective amount of composition or solid oral dosage form according to the invention to provide administration of active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

The term "modified release" as used herein in relation to the composition according to the invention or a rate controlling polymer or used in any other context means release, which is not immediate release and is taken to encompass controlled release, sustained release, prolonged release, timed release, retarded release, extended release and delayed release. The term "modified release dosage form" as used herein can be described as dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products (as per US FDA guideline for 'SUPAC-MR: Modified Release Solid Oral Dosage Forms').

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration.

The term "active ingredient" refers to an agent, active ingredient compound or other substance, or compositions and mixture thereof that provide some pharmacological, often beneficial, effect. Reference to a specific active ingredient shall include where appropriate the active ingredient and it's pharmaceutically acceptable salts.

The term "high solubility" as used herein in relation to high dose active agent means that from less than 1 part to 30 parts of the water will require dissolving 1 part of active ingredient.

The invention provides a novel modified release dosage form of high solubility active ingredient, which utilizes dual retard technique to effectively reduce the quantity of release controlling agents; a process for preparing the dosage form.

The dosage form comprises of a) Micro matrix particles containing high dose, high solubility active ingredient and one or more hydrophobic release controlling agent, b) Coating of Micro matrix particles with one or more hydrophobic release controlling agents. It may optionally

also include one or more commonly used excipients in oral pharmaceutical formulations. The release of high solubility active ingredient is controlled through dual retard technique. The dual retard technique is a combination of matrix formulations and reservoir formulations. First the micro matrix particles of high dose, high solubility dose active ingredient and one or more hydrophobic release controlling agents are formed and then these are further coated with one or more release controlling agents. Thus the dual retard release technique presents the double barriers and effectively controls the diffusion of the high solubility active ingredients from the present invention in predictable manner and also significantly reduces the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing. The other advantages of the present invention are such as it reduces the chances of dose dumping, unnecessary burst effects and failure of the system, which are otherwise usually associated with simple matrix or reservoir systems.

The high solubility active ingredient can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Further, high solubility active ingredient, where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

The high solubility active ingredients are comprises of the following therapeutic classes but not limited to anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritis, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants,

emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

Examples of high dose, high solubility active ingredients comprises of but not limited to captopril, ranitidine hydrochloride, potassium chloride, clindamycin, hydroxyurea, erythromycin lactobionate, vancomycin hydrochloride, balsalazide disodium, aminocaproic acid, lisinopril, tramadol, acetaminophen, ciprofloxacin, esters of ampicillin, sodium valproate, niacin, diltiazem, venlafaxine, isosorbide 5-imononitrate, isosorbide dinitrate, pentoxyphylline, propranolol, quetiapine. Other drugs suitable for use and meeting the solubility criteria described above will be apparent to those skilled in the art.

As indicated above the outer portion of the present invention may comprise auxiliary excipients such as for example lubricants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal slilcon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

In micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:1 to 100:75, more

particularly from 100:5 to 100:50, still more preferably from100:7.5 to 100:30 and most preferably from 100:10 to 100:20.

Micro matrix particles and coating of one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:0.5 to 100:75, more particularly from 100:2.5 to 100:50, still more preferably from100:5 to 100:30 and most preferably from 100:7.5 to 100:20.

According to one embodiment the release controlling agents are pharmaceutically excipients, which are hydrophobic in nature.

The polymers that can be used to form the rate-controlling membrane or micromatrix are described in greater detail herein below.

The hydrophobic release controlling agents are selected from but are not limited to Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, Polyacrylate dispersion 30% as described in Ph. Eur., Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly (hexyl methacrylate). Poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

According to an especially preferred embodiment the release controlling agents contains ammonio methacrylate co-polymers and fatty acid esters as hereinafter described.

The suitable hydrophobic agents are polymers sold under the Trade Mark Eudragit RS (Ammonio Methacrylate Copolymer type B USP),Eudragit NE 30D (Polyacrylate dispersion 30% Ph., Eur.) and Kollicoat SR 30 D and fatty acid esters such as

glyceryl behenate, and hydrogenated castor oil. Eudragit polymers are polymeric lacquer substances based on acrylate and/or methacrylates.

The dosage form can also include one or more commonly used excipients in oral pharmaceutical formulations.

Representative commonly used excipients in oral pharmaceutical formulations include talc, fumed silica, glyceryl monostearate, magnesium stearate, calcium stearate, kaolin, colloidal silica, gypsum, Tween 80, Geleol pastiles (trade mark), micronised silica and magnesium trisilicate.

The quantity of commonly used excipients in oral pharmaceutical formulations used is from about 2% to about 500% by weight, preferably from 2 to 100% more particularly 10 to 60% based on the total dry weight of the polymer.

The dosage form can also include a material that improves the processing of the release controlling agents. Such materials are generally referred to as "plasticisers" and include, for example, adipates, azelates, benzoates, citrates, isoebucaes, phthalates, sebacates, stearates, tartrates, polyhydric alcohols and glycols.

Representative plasticisers include acetylated monoglycerides; butyl phthalyl butyl gylcolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate,; ethyl phthalyl ethyl glycolate; glycerin; ethylene glycol, propylene glycol; Triethyl citrate; triacetin; tripropinoin; diacetin; dibutyl phthalate; acetyl monoglyceride; polyethylene glycols; castor oil; triethyl citrate; polyhydric alcohols, acetate esters, glycerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisoctyl trimellitate, diethylexyl phthalate, di-n-octyl phthalate, di-I-octyl phthalate, di-I-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylexyl trimellitate, di-2-ethylexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, glyceryl monocaprylate, glycerol distearate and glyceryl monocaprate.

The amount of plasticiser to be used is from about 1% to 50%based on the weight of the dry release controlling agent(s).

The amount of release controlling agent(s) to be used in forming the outer portion will be determined based on

various parameters such as the desired delivery properties, including the amount of active ingredient to be delivered, the active ingredient release rate desired, and the size of the micro matrix particles.

The novel modified release dosage form of the present invention can be manufactured by the following procedure: The micro matrix particles can be manufactured in accordance with usual techniques in which the active ingredient and one or more hydrophobic release controlling agents are mixed and granulated by adding solvent in a low or high shear mixer or by fluidized bed granulator. The granulate is dried, preferably in a fluidized bed dryer. The dried granulate is sized. Alternatively the micro matrix particles can be made by extrusion, spheronization or by roller compaction. The micro matrix particles can be coated by a solution of one or more hydrophobic release controlling agents by any known method, including spray application. Spraying can be carried out using a fluidized bed coated (preferably Wurster coating), or in a pan coating system. Alternatively the coating of the micro matrix particles with one or more rate controlling agents can be done by hot melt process using a granulator or fluidized bed coated (preferably Wurster coating), or in a pan coating system. The compression of tablets is carried out on usual compression machines (e.g. machines of the Manesty, Cadmach or Kilian). The tablets can be made of various sizes and shapes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 (a) is a cross section of coated micro matrix particles prepared by spheronization and coating for the purpose of illustration only.

FIG. 1 (b) is a cross section of coated micro matrix particles prepared by granulation and coating for the purpose of illustration only.

FIG. 2 is a plot of % active ingredient *versus* time for modified release active agent prepared using dual retard technique as described in the present invention and prepared without retard release technique as per examples 1 and 3;

FIG. 3 is a plot of % active ingredient *versus* time for modified release active agent prepared using dual retard technique as described in the present invention and

prepared without retard release technique as per examples 2 and 4.

FIG. 1 (a) and 1(b) show the cross section of the coated micro matrix particles 1 as described in the present invention and having 2 a high solubility active ingredient, 3 hydrophobic release controlling agent and 4 a coating of hydrophobic release controlling agent. FIG. 2 and 3 shows release of high dose, high solubility active agent 5 & 6 and 9 & 10 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique and release of high solubility active agent 7 & 8 and 11 & 12 as per example 3 & 4 respectively from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms inspite of that the figures clearly shows that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high dose, high solubility active ingredient for prolonged period.

DIFFERENT MODES FOR PRACTICING THE INVENTION

The following examples further illustrate but by no means limit the present invention.

The dissolution of novel dosage form of the present invention was determined by following method.

For sodium valproate-

Instrument	-	Apparatus I, USP (basket)
Revolution	-	60 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	1000 ml pH 6.8 buffer

For niacin-

Instrument	-	Apparatus I, USP (Basket)
Revolution	-	100 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	900 ml 0.1 N HCl

EXAMPLES

EXAMPLE 1

A) Micro matrix particles- 90.91 %w/w of sodium valproate is mixed with 9.09 %w/w of Eudragit RS (Ammonio Methacrylate Copolymer type B USP) and the mixture is

granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

B) Coating of Micro matrix particles- 85.54 %w/w of micro matrix particles is charged in fluidized bed process of wurster type (manufactured by Glatt, Germany), GPCG-3. 13.61 %w/w of hydrogenated castor oil is dissolved in acetone and this coating solution is sprayed to coat the micro matrix particles. The coated micro matrix particles are sieved and mixed with 0.86 %w/w magnesium stearate.

C) Compression of tablets
Tablet (1)- 1286 mg granules are pressed to tablet (equivalent to 1000 mg sodium valproate) using 20.3 X 9.8 mm oval punches.

Tablet (2)- 643 mg granules are pressed to tablet(equivalent to 500 mg sodium valproate) using 14.95 X 8.35 mm oblong punches.

The dissolution rate of the novel dosage form was determined (Table 1)

Table 1: Dissolution profile

Time (hour)	% Released	
	Tablet (1)	Tablet (2)
1	18,2	23.4
2	27,8	35.1
4	42,5	51.5
6	52,8	62.9
8	61,6	72.1
10	68,3	79.2
12	74,2	84.1
14	79,2	88.3
24	94,4	102.0

EXAMPLE 2

A) Micro matrix particles- 90.91 %w/w of niacin is mixed with 9.09 %w/w of Eudragit RS (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

B) Coating of Micro matrix particles- 85.54 %w/w of micro matrix particles is charged in fluidized bed process of wurster type (manufactured by Glatt, Germany), GPCG-3. 13.61 %w/w of hydrogenated castor oil is dissolved in acetone and this coating solution is sprayed to coat the

micro matrix particles. The coated micro matrix particles are sieved and mixed with 0.86 %w/w magnesium stearate.

C) Compression of tablets

Tablet (1)- 1286 mg granules are pressed to tablet (equivalent to 1000 mg niacin) using 20.3 X 9.8 mm oval punches.

Tablet (2)- 643 mg granules are pressed to tablet (equivalent to 500 mg niacin) using 14.95 X 8.35 mm oblong punches.

The dissolution rate of the novel dosage form was determined (Table 2)

Table 2: Dissolution profile

Time (hour)	% Released	
	Tablet (1)	Tablet (2)
1	9.1	12.0
2	14.6	18.2
4	23.8	28.6
6	27.5	35.2
8	30.6	39.5
10	34.7	44.8
12	37.6	49.5
14	43.8	52.5
24	50.3	64.5

Dosage forms described in the examples 3 and 4 are prepared by not coating the micro matrix particles but the hydrophobic release controlling agent is mixed with the micro matrix particles. The sole purpose of these examples is to demonstrate the usefulness of the present invention as described earlier. The examples clearly show that the rate of release of the modified release active ingredient is significantly faster than the present invention.

EXAMPLE 3

77.76 %w/w of sodium valproate is mixed 7.78 %w/w of Eudragit RS (Ammonio Methacrylate Copolymer type B USP) and

the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.6 %w/w of hydrogenated castor oil and 0.86 %w/w of magnesium stearate.

Compression of tablets

Tablet (1)- 1286 mg granules are pressed to tablet (equivalent to 1000 mg sodium valproate) using 20.3 X 9.8 mm oval punches.
Tablet (2)- 643 mg granules are pressed to tablet (equivalent to 500 mg sodium valproate) using 14.95 X 8.35 mm oblong punches.
The dissolution rate of the novel dosage form was determined (Table 3)

Table 3: Dissolution profile

Time (hour)	% Released	
	Tablet (1)	Tablet (2)
1	63.4	50.2
2	85.1	69.1
4	101.6	92.0
6	103.1	102.5

EXAMPLE 4

77.76 %w/w of niacin is mixed with 7.78 %w/w of Eudragit RS (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.6 %w/w of hydrogenated castor oil and 0.86 %w/w of magnesium stearate.

Compression of tablets
Tablet (1)- The granules are pressed to 1286 mg (equivalent to 1000 mg niacin) are compressed using 20.3 X 9.8 mm oval punches.
Tablet (2)- The granules are pressed to 643 mg (equivalent to 500 mg niacin) are compressed using 14.95 X 8.35 mm oblong punches.
The dissolution rate of the novel dosage form was determined (Table 4)

Table 4: Dissolution profile

Time (hour)	% Released	
	Tablet (1)	Tablet (2)
1	31.9	29.6
2	44.8	34.9
4	60.3	51.7
6	71.7	62.1
8	81.4	67.7
10	88.2	74.7
12	94.7	82.3
24	98.6	98.1

Dated this the 21st day of January 2003.

H. SUBRAMANIAM
Of Subramaniam, Nataraj & Associates
Attorneys for the Applicants

ABSTRACT

A novel modified release dosage form comprising of a high solubility active ingredient, which utilizes dual retard technique to effectively reduce the quantity of release controlling agents; a process for preparing the dosage form.

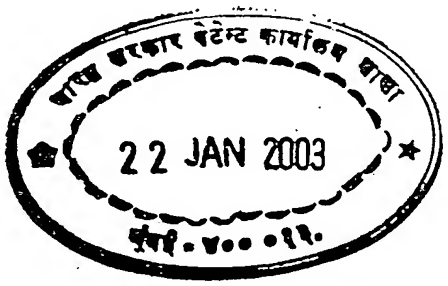


FIG.1 (a)

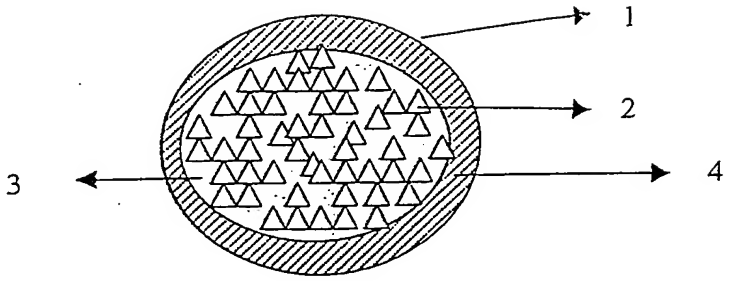


FIG.1 (b)

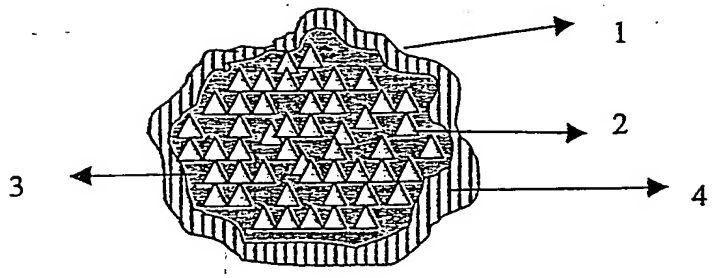


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FIG. 2

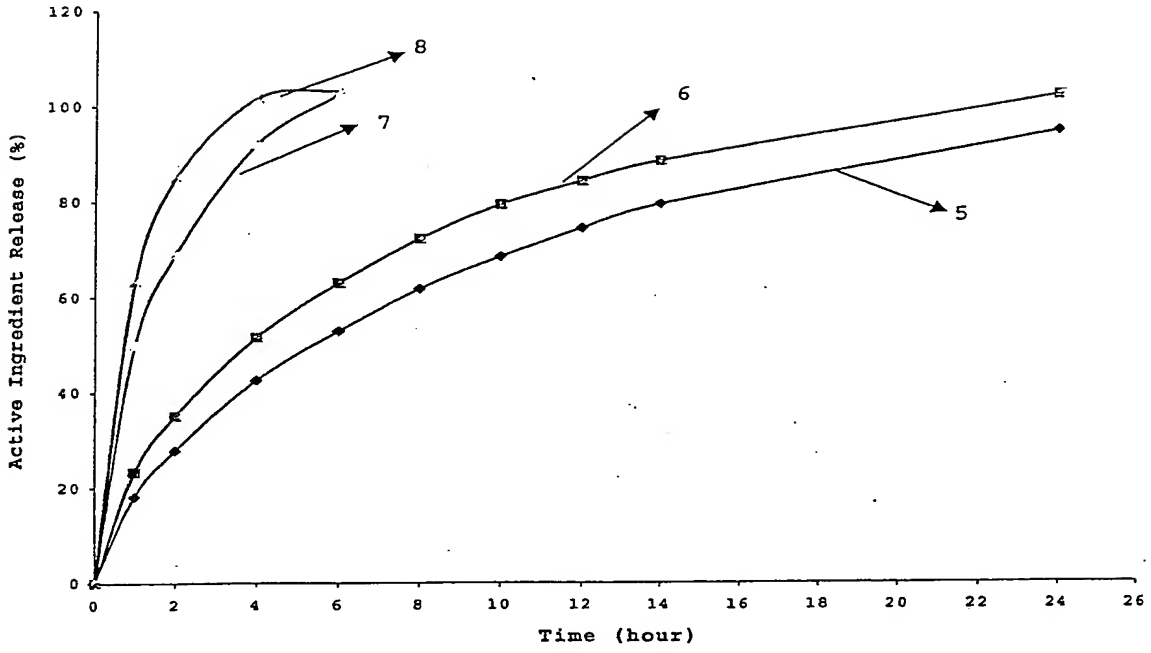

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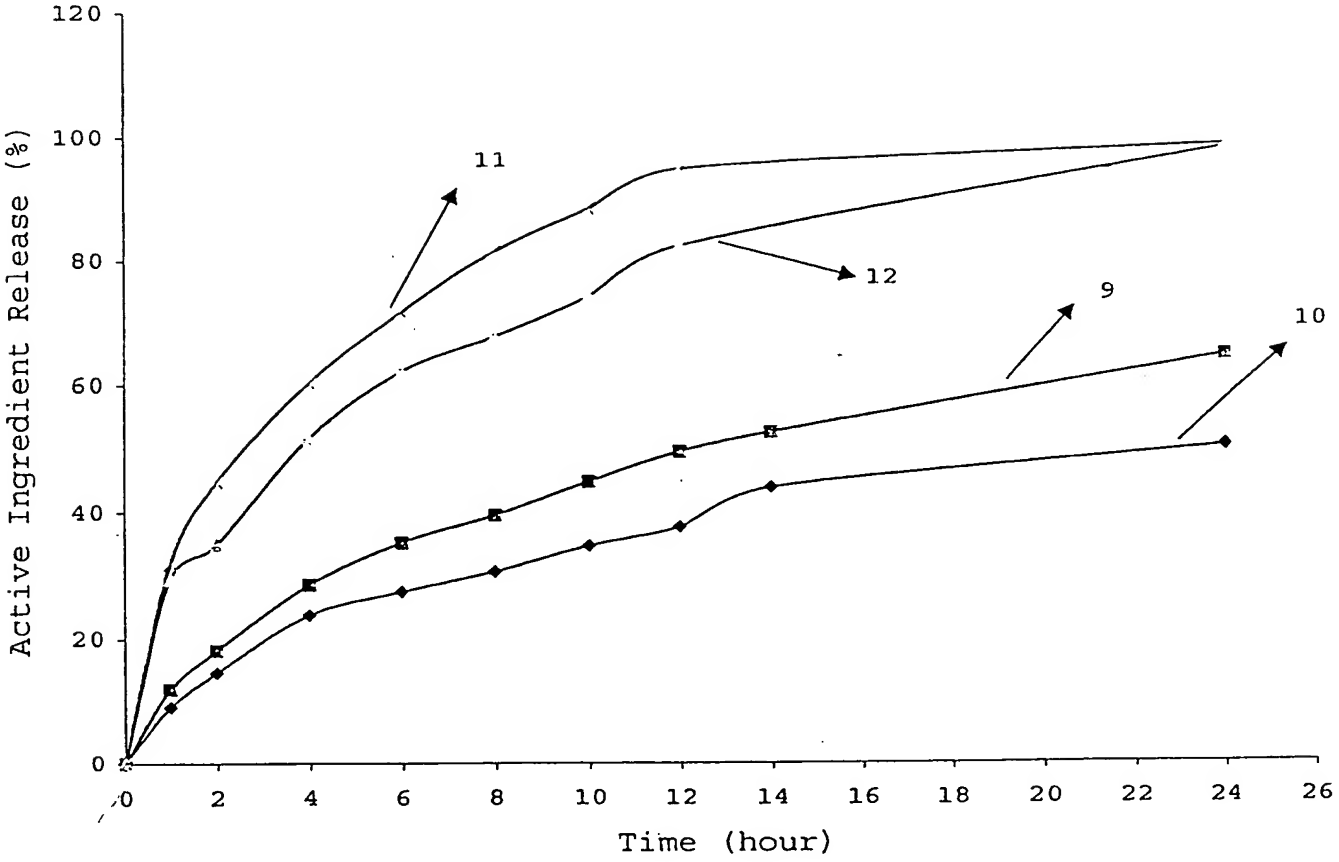
FIG.3



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